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1/77

Request for grant of a patent

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The Patent Office
Cardiff Road
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1. Your reference — KR/JW/P32292

2. Patent application number
(The Patent Office will fill in his part) — **9909473.2**

26APR99 E442526-1 D02029
01/7700 0.00 - 9909473.2

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

SmithKline Beecham plc
New Horizons Court, Brentford, Middx TW8 9EP,
Great Britain

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — 7605058001

4. Title of the invention — Novel Compounds

5. Name of your agent *(if you have one)*

CORPORATE INTELLECTUAL PROPERTY

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

SMITHKLINE BEECHAM PLC
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP

Patents ADP number *(if you know it)* — 58009740004

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

Patents Form 1/77

9. Enter number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	5
Claim(s)	
Abstract	
Drawings	3

10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 1/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature K Rutter Date 23-Apr-99

K Rutter

12. Name and daytime telephone number of person to contact in the United Kingdom

K Rutter 01279 644396

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NOVEL PHARMACEUTICAL

This invention relates to a novel pharmaceutical, to a process for the preparation of the pharmaceutical and to the use of the pharmaceutical in medicine.

International Patent Application, Publication Number WO94/05659 discloses certain thiazolidinedione derivatives having hypoglycaemic and hypolipidaemic activity including 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt (hereinafter also referred to as "Compound (I)").

It has now been discovered that Compound (I) exists in a novel polymorphic form which is particularly suitable for bulk preparation and handling. The novel form can be prepared by an efficient, economic and reproducible process particularly suited to large scale preparation.

The novel polymorphic form ('the Polymorph') also has useful pharmaceutical properties and in particular it is indicated to be useful for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

Accordingly, the present invention provides a polymorphic form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt characterised in that it provides:

(i) an infrared spectrum substantially in accordance with Figure I;

(ii) a Raman spectrum substantially in accordance with Figure II; and /or

(iii) an X-ray powder diffraction (XRPD) pattern substantially in accordance with Figure III.

The present invention encompasses the Polymorph isolated in pure form or when admixed with other materials, for example the known forms of Compound I or any other material.

Thus in one aspect there is provided the Polymorph in isolated form.

In a further aspect there is provided the Polymorph in pure form.

In yet a further aspect there is provided the Polymorph in crystalline form.

The invention also provides a process for preparing the Polymorph, characterised in that a solution of Compound (I) in denatured ethanol at an elevated temperature, for example 50°C, is seeded with the Polymorph then cooled to 20-25°C to provide the Polymorph. The Polymorph is then recovered from the denatured ethanol.

The solution of Compound (I) in the denatured ethanol is conveniently prepared by dissolving Compound (I) in the required amount of denatured ethanol at an elevated temperature, for example 60°C.

Conveniently the Polymorph is recovered from the denatured ethanol by filtration and subsequent drying.

Compound (I) is prepared according to known procedures, such as those disclosed in WO94/05659. The disclosures of WO94/05659 are incorporated herein by reference.

When used herein "denatured ethanol" means ethanol containing small amounts of methanol for example ethanol containing 4%v/v of methanol.

When used herein the term 'prophylaxis of conditions associated with diabetes mellitus' includes the treatment of conditions such as insulin resistance, impaired glucose tolerance, hyperinsulinaemia and gestational diabetes.

Diabetes mellitus preferably means Type II diabetes mellitus.

Conditions associated with diabetes include hyperglycaemia and insulin resistance and obesity. Further conditions associated with diabetes include hypertension, cardiovascular disease, especially atherosclerosis, certain eating disorders, in particular the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating ,such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia. Additional conditions associated with diabetes include polycystic ovarian syndrome and steroid induced insulin resistance.

The complications of conditions associated with diabetes mellitus encompassed herein includes renal disease, especially renal disease associated with the development of Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

As mentioned above the compound of the invention has useful therapeutic properties: The present invention accordingly the Polymorph for use as an active therapeutic substance.

More particularly, the present invention provides the Polymorph for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

The Polymorph may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier. The formulation of the Polymorph and dosages thereof are generally as disclosed for Compound (I) in International Patent Application, Publication Number WO94/05659.

Accordingly, the present invention also provides a pharmaceutical composition comprising the Polymorph and a pharmaceutically acceptable carrier therefor.

The Polymorph is normally administered in unit dosage form.

The active compound may be administered by any suitable route but usually by the oral or parenteral routes. For such use, the compound will normally be employed in the form of a pharmaceutical composition in association with a pharmaceutical carrier, diluent and/or excipient, although the exact form of the composition will naturally depend on the mode of administration.

Compositions are prepared by admixture and are suitably adapted for oral, parenteral or topical administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, pastilles, reconstitutable powders, injectable and infusable solutions or suspensions, suppositories and transdermal devices. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

Solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending

on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the active compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the active compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active compound.

In addition such compositions may contain further active agents such as anti-hypertensive agents and diuretics.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The present invention further provides a method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of the Polymorph to a human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof the Polymorph may be taken in doses, such as those described above.

Similar dosage regimens are suitable for the treatment and/or prophylaxis of non-human mammals.

In a further aspect the present invention provides the use of the Polymorph for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

No adverse toxicological effects are indicated in the above mentioned treatments for the compounds of the invention.

The following example illustrates the invention but do not limit it in any way.

Characterising data

Infrared

The infrared absorption spectrum of a mineral oil dispersion of the Polymorph was obtained using a Nicolet 710 FT-IR spectrometer at 2 cm^{-1} resolution. Data were digitised at 1 cm^{-1} intervals. The spectrum obtained is shown in Figure I.

Raman

The Raman spectrum of the Polymorph was recorded through a glass vial using a Perkin Elmer 2000R spectrometer at 4 cm^{-1} resolution and is shown in Figure II. Excitation was achieved using a Nd:YAG laser (1064 nm) with a power output of 500 mW.

X-Ray Powder Diffraction (XRPD)

The XRPD pattern of the Polymorph is shown in Figure III and a summary of the XRPD angles and calculated lattice spacings characteristic of the Polymorph is given in Table I.

A Bruker AXS D8 Advance X-ray powder diffractometer (Cu X-ray source) was used to generate the pattern using the following acquisition conditions:

Tube anode:	Cu
Generator tension:	40 kV
Generator current:	40 mA
Start angle:	2.0 °2θ
End angle:	35.0 °2θ
Step size:	0.02 °2θ
Time per step:	2.5s

Figure I: Infrared Spectrum of the Polymorph

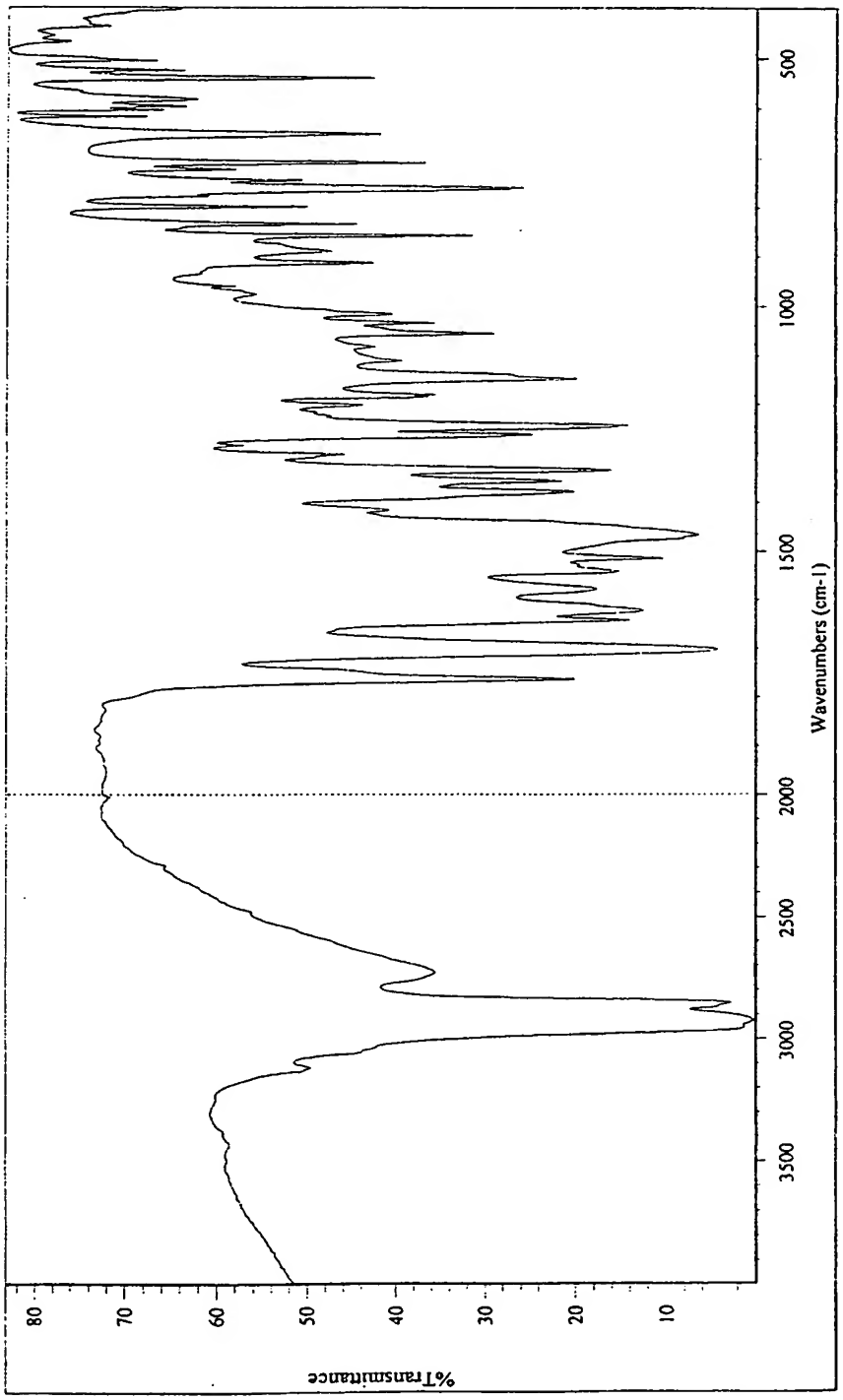


Figure II: Raman Spectrum of the Polymorph

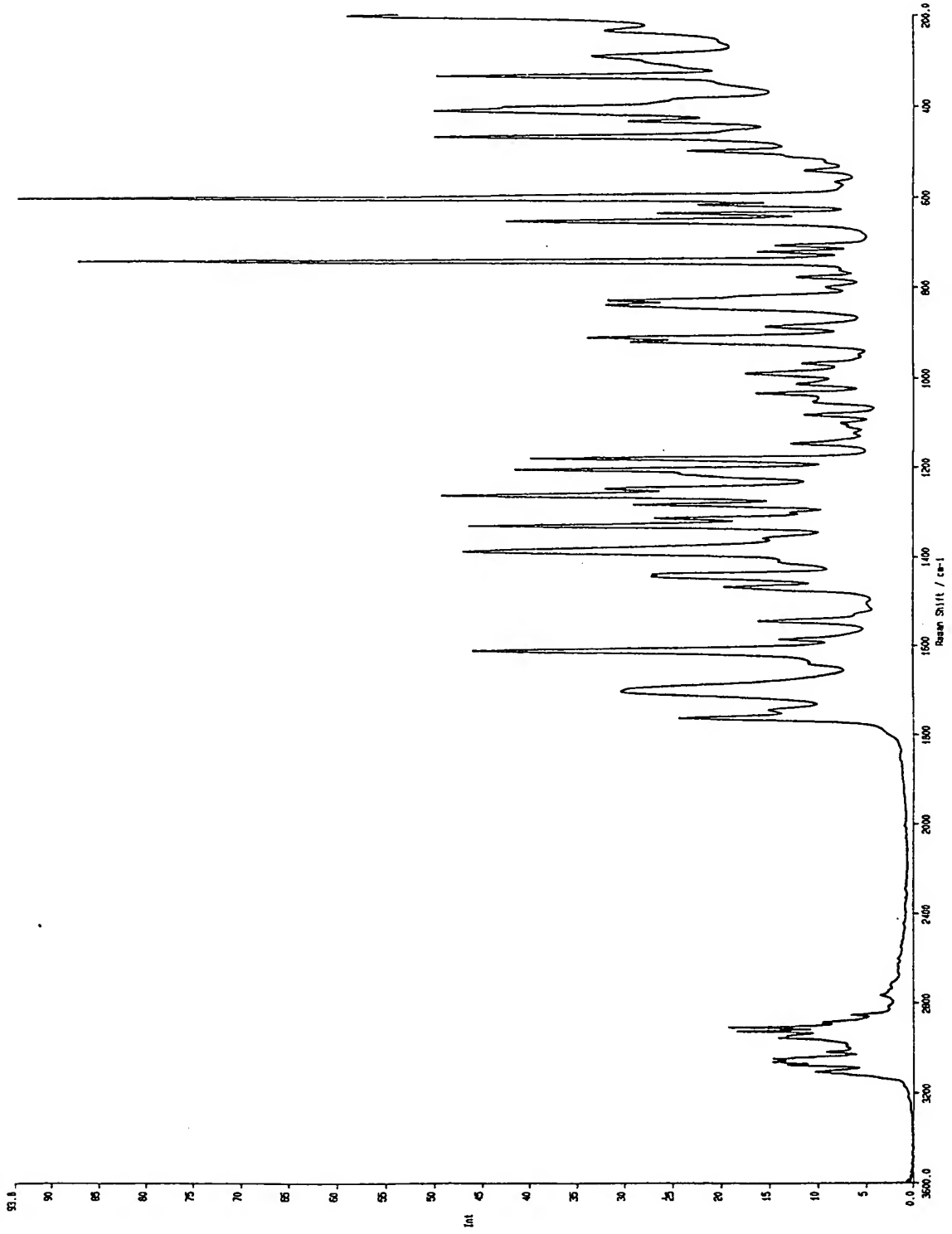
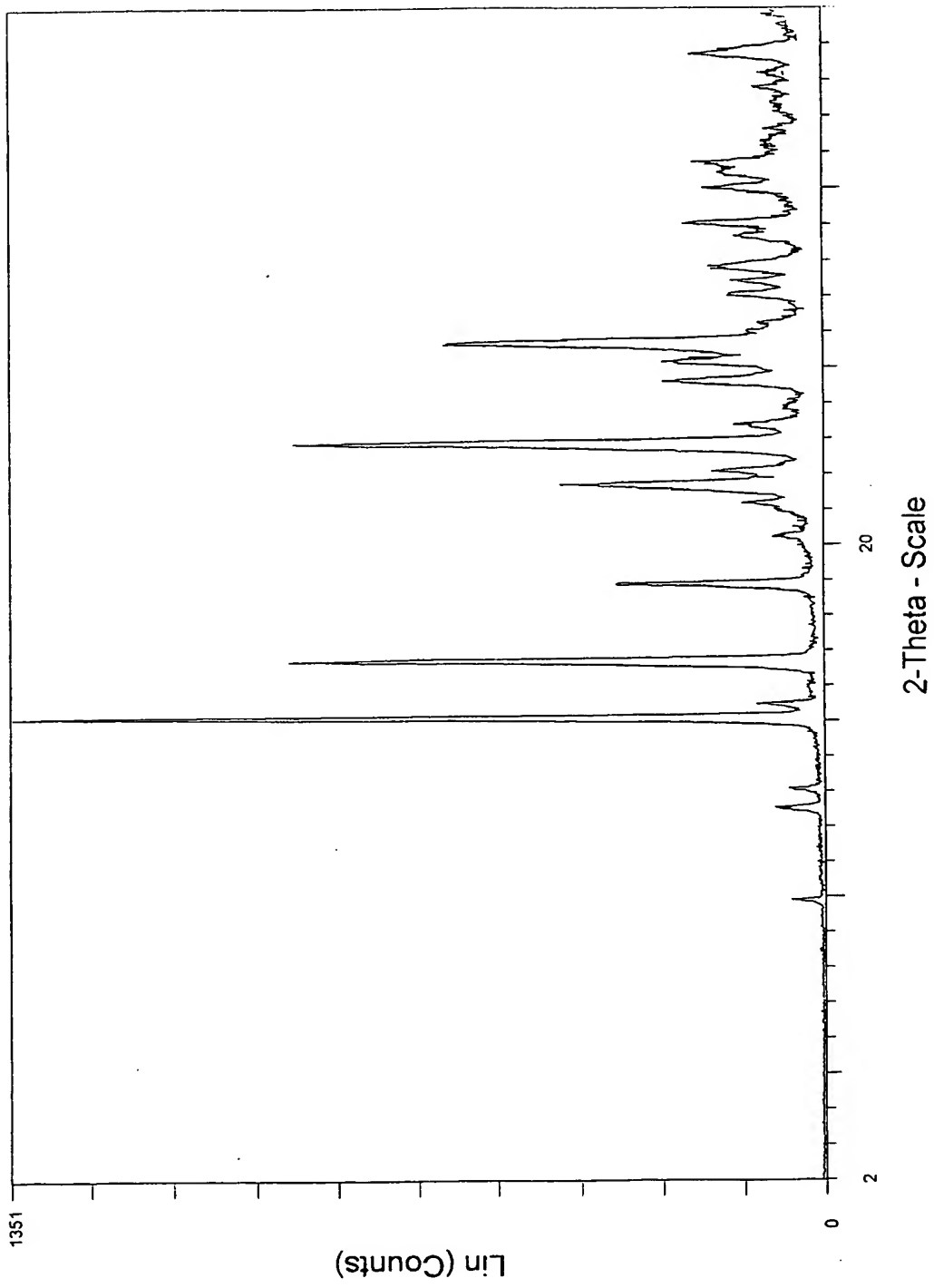


Fig III: X-Ray Powder Diffraction Pattern of the Polymorph



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